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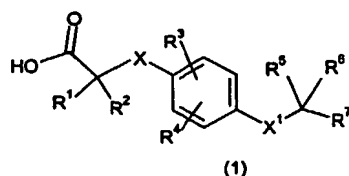
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SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
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Published:

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For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: PHENYLALKANOIC ACID AND PHENYLOXYALKANOIC ACID DERIVATIVES AS HPPAR ACTIVATORS



(57) Abstract: The present invention provides a compound of formula (I): wherein: R1 and R2 are independently H or C1-3 alkyl; X represents a O or (CH2)_n where n is 0, 1 or 2; R3 and R4 independently represent H, C1-3 alkyl, -OCH3, -CF3, allyl, or halogen; X1 represents O, S, SO2, SO, or CH2; R5 and R6 independently represent hydrogen, C1-6 alkyl (including branched alkyl and optionally substituted by one or more halogens or C1-6alkoxy), or together with the carbon atom to which they are bonded form a 3-6 membered cycloalkyl ring; R7 represents a phenyl or a 6 membered heteroaryl group containing 1, 2 or 3 nitrogen atoms wherein the phenyl or heteroaryl group is substituted by 1, 2 or 3 moieties selected from the group consisting of halogen, C1-6 alkoxy, C1-6 alkyl, CF3, hydroxy, or phenyl (which may be optionally substituted by one or more C1-3 alkyl, -OC1-3 alkyl, CN, acetyl, hydroxy, halogen or CF3).

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 03/06415

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/44 A61K31/192 A61P9/10 A61P3/10 A61P3/06
C07C323/20 C07D213/30 C07D213/32 C07C59/66 C07C59/68
C07D213/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 11255 A (ONO PHARMACEUTICAL CO., LTD., JAPAN) 11 March 1999 (1999-03-11) see compounds 26-157, 26-158 page 200; table 26 see compounds 26-196 and 26-197 page 201; table 27 page 192 see compounds 26-299 - 26-302 page 204	1-21
X	WO 00 64876 A (MCGEEHAN GERARD M ;MORRIS ROBERT (US); ZHANG LITAO (US); BOBKO MAR) 2 November 2000 (2000-11-02) claims 1,50-88	1-21
A	EP 1 067 109 A (ONO PHARMACEUTICAL CO) 10 January 2001 (2001-01-10) the whole document	1-21
	-/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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- * & * document member of the same patent family

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/06415

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 31907 A (CALLAGHAN JOHN MARK O ;GLAXO GROUP LTD (GB); COBB JEFFREY EDMOND () 4 September 1997 (1997-09-04) the whole document	1-21
X	EP 1 132 376 A (TAKEDA CHEMICAL INDUSTRIES, LTD., JAPAN) 12 September 2001 (2001-09-12) see formula (IV) page 18, line 1-9 page 37, line 1-24	1,13
P,X	GENTLES, ROBERT G. ET AL: "Standardization Protocols and Optimized Precursor Sets for the Efficient Application of Automated Parallel Synthesis to Lead Optimization: A Mitsunobu Example" JOURNAL OF COMBINATORIAL CHEMISTRY (2002), 4(5), 442-456 , XP002255800 page 454, left-hand column	1,13
P,X	EP 1 283 039 A (TAKEDA CHEMICAL INDUSTRIES, LTD., JAPAN) 12 February 2003 (2003-02-12) page 27; example 4 see formula (IV) page 21, line 5	1,13
X	& WO 01 087293 A 22 November 2001 (2001-11-22)	1,13
X	WO 01 36351 A (LEWIS RONALD D II ;CORVAS INT INC (US); DUNCAN DAVID F (US); MADIS) 25 May 2001 (2001-05-25) claims; figures 1H,1J,2K,,2L,2V; examples 3,4	1-12
X	KUCHAR M ET AL: "BENZYLOXYARYLALIPHATIC ACIDS: SYNTHESIS AND QUANTITATIVE RELATIONS BETWEEN STRUCTURE AND ANTIINFLAMMATORY ACTIVITY" COLLECTION OF CZECHOSLOVAK CHEMICAL COMMUNICATIONS, ACADEMIC PRESS, LONDON, GB, vol. 47, 1982, pages 2514-2524, XP001002034 ISSN: 0010-0765 examples	1-12

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/06415

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>KUCHAR M ET AL: "THE EFFECTS OF LIPOPHILICITY ON THE INHIBITION OF DENATURATION OF SERUM ALBUMIN AND ON THE ACTIVATION OF FIBRINOLYSIS OBSERVED WITH A SERIES OF BENZYLOXYARYLALIPHATIC ACIDS" COLLECTION OF CZECHOSLOVAK CHEMICAL COMMUNICATIONS, ACADEMIC PRESS, LONDON, GB, vol. 48, 1983, pages 1077-1088, XP001002033 ISSN: 0010-0765 examples</p>	1-12
X	<p>US 4 221 919 A (GRIMOVA JAROSLAVA ET AL) 9 September 1980 (1980-09-09) examples</p>	1-12

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

Continuation of Box I.2

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search has been restricted to claim 13.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/06415

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 20 and 21 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/06415

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9911255	A	11-03-1999	AU 8750298 A WO 9911255 A1	22-03-1999 11-03-1999
WO 0064876	A	02-11-2000	AU 4807000 A BR 0010126 A CA 2371308 A1 CN 1356983 T CZ 20013834 A3 EE 200100558 A EP 1177176 A1 HR 20010793 A1 HU 0200997 A2 JP 2002543065 T NO 20015226 A PL 351470 A1 SK 15522001 A3 WO 0064876 A1 ZA 200108800 A	10-11-2000 26-02-2002 02-11-2000 03-07-2002 17-04-2002 16-12-2002 06-02-2002 28-02-2003 29-07-2002 17-12-2002 05-12-2001 22-04-2003 04-06-2002 02-11-2000 10-02-2003
EP 1067109	A	10-01-2001	AU 3275999 A EP 1067109 A1 US 6506757 B1 WO 9946232 A1 US 2003153579 A1	27-09-1999 10-01-2001 14-01-2003 16-09-1999 14-08-2003
WO 9731907	A	04-09-1997	AP 780 A AT 205485 T AU 717699 B2 AU 2093597 A BG 102792 A BR 9707786 A CA 2247443 A1 CN 1218460 A , B CZ 9802750 A3 DE 69706658 D1 DE 69706658 T2 DK 888317 T3 EA 1403 B1 EE 9800288 A WO 9731907 A1 EP 0888317 A1 ES 2163125 T3 HK 1015369 A1 HR 970110 A1 HU 0004845 A2 IL 125796 A JP 3255930 B2 JP 2000507216 T NO 983940 A NZ 331381 A PL 328871 A1 PT 888317 T SI 888317 T1 SK 116398 A3 TR 9801707 T2 US 6294580 B1 ZA 9701645 A	22-11-1999 15-09-2001 30-03-2000 16-09-1997 31-08-1999 27-07-1999 04-09-1997 02-06-1999 13-01-1999 18-10-2001 20-06-2002 21-01-2002 26-02-2001 15-02-1999 04-09-1997 07-01-1999 16-01-2002 15-02-2002 30-04-1998 28-05-2001 14-06-2001 12-02-2002 13-06-2000 27-10-1998 23-06-2000 01-03-1999 28-03-2002 30-04-2002 13-04-1999 21-12-1998 25-09-2001 10-12-1997

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/06415

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 1132376	A	12-09-2001	AU 1183300 A CA 2351692 A1 EP 1132376 A1 US 6586475 B1 WO 0031021 A1 JP 2000212076 A	13-06-2000 02-06-2000 12-09-2001 01-07-2003 02-06-2000 02-08-2000
EP 1283039	A	12-02-2003	AU 5877101 A CA 2407088 A1 EP 1283039 A1 CN 1438883 T WO 0187293 A1 JP 2002037731 A	26-11-2001 22-11-2001 12-02-2003 27-08-2003 22-11-2001 06-02-2002
WO 0136351	A	25-05-2001	AU 1624801 A WO 0136351 A2	30-05-2001 25-05-2001
US 4221919	A	09-09-1980	CS 175831 B1 AT 341506 B AT 953075 A BE 836679 A1 CA 1074330 A1 CH 619205 A5 DE 2556474 A1 DK 573475 A ,B, FI 753551 A ,B, FR 2294689 A1 GB 1487149 A JP 51086442 A NL 7514725 A SE 427108 B SE 7514212 A	31-05-1977 10-02-1978 15-06-1977 16-04-1976 25-03-1980 15-09-1980 01-07-1976 18-06-1976 18-06-1976 16-07-1976 28-09-1977 29-07-1976 21-06-1976 07-03-1983 18-06-1976